UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,217	02/26/1999	MARK T. KEATING	2323-127	3509

6449 7590 01/17/2003

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/17/2003 30

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/258,217	Applicant(s) Keating et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 3, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5, 9, and 10* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 9, and 10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-3-02 has been entered.

Applicants' amendment filed 12-3-02 has been entered. Claim 6 has been canceled. Claim 2 has been amended. Claims 1-5, 9 and 10 are pending and under consideration.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on naturally occurring mice, which are not considered patentable subject matter. See MEP. 2105. This rejection could be overcome by amending the claims to recite a "a transgenic mouse".

3. Claims 3 and 4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on naturally occurring mouse cells,

which are not considered patentable subject matter. See MEP. 2105. This rejection could be overcome by amending the claims to recite a "an isolated mouse cell".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 5, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "SVAS" in claims 5, 9 and 10 is vague and renders the claims indefinite. SVAS can be abbreviation for various meanings. Spelling out the term "SVAS" as "supravalvular aortic stenosis" would be remedial.

The term "ELN+/- mouse" bridging lines 2 and 3 of claim 9 and the term "mouse" in line 3 of claim 9 are vague and render the claim indefinite. There is a "ELN+/- mouse" in line 2 of claim 9, it is unclear whether the "ELN+/- mouse" bridging lines 2 and 3 is the same as the "ELN+/- mouse" in line 2 of claim 9. It is also unclear what "mouse" is intended in line 3 of claim 9. It seems applicants intend to claim "ELN+/- mouse cell" in both situations. Changing "ELN+/- mouse" and "mouse" to "ELN+/- mouse cell" would be remedial.

The term "elastin" in line 6 of claim 10 is vague and renders the claim indefinite. "Elastin" could mean elastin protein or elastin DNA or elastin mRNA. It is unclear what is intended to be claimed.

6. Claim 9 recites the limitation "said organisms" in line 7 of claim 9. There is insufficient antecedent basis for this limitation in the claim. The claim only mentions human or mouse but does not recite "organisms".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keating, 1997 (Cardiovascular research, Vol. 36, p. 134-137, IDS-AB) in view of Wydner et al., 1994 (X2).

Claims 3 and 4 are directed to a mouse cell comprising one functional elastin gene and either one nonfunctional or no second mouse elastin gene, comprising no functional elastin gene in its genome.

Keating teaches that SVAS is a common feature of Williams syndrome (WS), and WS is "associated with submicroscopic deletions of chromosome 7q11.23; inherited or de novo

constitutional deletion of one elastin allele was identified in every WS patient studied, indicating that hemizygosity...at this locus is the mechanism of vascular and connective tissue pathology". Keating suggests that "developmental reduction in elastin can lead to vascular obstruction, hypertension, premature aging of skin, and other connective tissue abnormalities". Keating teaches that "in WS patients the elastin gene should be missing from one homologue of chromosome 7" and suggests breeding mice with targeted knockout elastin gene to determine clinical consequences in the animal model (e.g. p. 136).

Keating does not teach the availability of mouse elastin gene for making a mouse containing knocked out elastin gene.

Wydner teaches the complete cDNA sequence of mouse tropoelastin (elastin) gene and the mutations in the tropoelastin gene are strongly implicated in supravalvular aortic stenosis (SVAS), a heritable vascular disorder that maps to chromosome 7 (e.g. introduction, p. 128, 129).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the cDNA sequence of mouse elastin gene as taught by Wydner to generate a mouse lacking one or both elastin gene because Keating teaches deletion of one elastin gene in human WS patient and suggests making mouse model having knocked out elastin gene. The mouse lacking one or both elastin gene would have mouse cells comprising only one functional elastin gene or no functional elastin gene in its genome.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to breed mice with targeted knockout elastin gene to determine clinical consequences in the animal model regarding WS or SVAS and to study the effect of elastin gene on vascular obstruction, hypertension, premature aging of skin, and other connective tissue abnormalities with reasonable expectation of success.

9. Claims 5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reitamo et al., 1994 (V) in view of Keating, 1997 (Cardiovascular research, Vol. 36, p. 134-137, IDS-AB) in view of Wydner et al., 1994 (X2).

Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using an ELN +/- mouse or human, wherein said drug candidates inhibit occlusion of arteries. Claims 9 and 10 are directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- mouse or human, or ELN +/- mouse or human cells and by measuring the synthesis of elastin RNA and elastin, respectively.

Reitamo teaches generating transgenic mice expressing a human elastin promoter/CAT reporter gene construct and injecting IL-10 subcutaneously into said transgenic mice. Reitamo et al. also teach a method of screening a compound which can stimulate the elastin promoter *in vivo or in vitro,* and show IL-10 up-regulates elastin gene expression *in vivo* by CAT assay (transgenic

mice skin) and *in vitro* by measuring the elastin mRNA level using Northern analysis (e.g. abstract, p. 332).

Reitamo does not teach using human or ELN +/- cells having only one functional elastin gene to screen drug candidate useful for treating atherosclerosis hypertension or SVAS in a human by measuring the synthesis of elastin or screen drug which inhibits occlusion of arteries.

Keating teaches that SVAS is a common feature of Williams syndrome (WS), and WS is "associated with submicroscopic deletions of chromosome 7q11.23; inherited or de novo constitutional deletion of one elastin allele was identified in every WS patient studied, indicating that hemizygosity...at this locus is the mechanism of vascular and connective tissue pathology". Keating suggests that "developmental reduction in elastin can lead to vascular obstruction, hypertension, premature aging of skin, and other connective tissue abnormalities". Keating teaches that "in WS patients the elastin gene should be missing from one homologue of chromosome 7" and suggests breeding mice with targeted knockout elastin gene to determine clinical consequences in the animal model (e.g. p. 136).

Wydner teaches the complete cDNA sequence of mouse tropoelastin (elastin) gene and the mutations in the tropoelastin gene are strongly implicated in supravalvular aortic stenosis (SVAS), a heritable vascular disorder that maps to chromosome 7 (e.g. introduction, p. 128, 129).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the transgenic mice as taught by Reitamo with the WS patient having one deleted

elastin gene and the mouse cells having only one functional elastin gene as taught by Keating and Wydner because Keating and Wydner teach that reduction of elastin gene function is associated with SVAS, WS, vascular obstruction, hypertension, premature aging of skin, and other connective tissue abnormalities. It would have been obvious for one of ordinary skill to use the WS patient having one deleted elastin gene and the mouse cells having only one functional elastin gene as taught by Wydner and Keating to screen for drugs or compounds useful for treating humans with SVAS, hypertension or atherosclerosis which are diseases associated with arteries.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to study the role of elastin gene on vascular obstruction, hypertension, premature aging of skin, and other connective tissue abnormalities, and in analogous human disorder such as SVAS and WS because SVAS and WS are the result of mutation or deletion of the elastin (ELN) gene and experiments with WS patient or mouse cells having only one functional elastin gene will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease. One having ordinary skill at the time the invention was made would have been motivated to use WS patient or mouse cells having only one functional elastin gene as taught by Wydner and Keating to screen for drugs or compounds useful for treating SVAS, atherosclerosis or hypertension in a human by measuring the synthesis of elastin mRNA or elastin, or the drug or compound which can inhibit the occlusion of arteries because the implication of the correlation of SVAS, WS, hypertension and

atherosclerosis with the elastin gene, and the discovery of such compounds would have been useful for treating humans with WS, SVAS, hypertension or atherosclerosis.

Conclusion

No claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.